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THE EFFECT ON ANTIBODY PRODUCTION OF THE REMOVAL OF VARIOUS ORGANS *

LUDVIG HEKTOEN AND ARTHUR R. CURTIS

From the Memorial Institute for Infectious Diseases, Chicago

Various methods have been used in the study of the problem of where in the body the antibodies are formed that develop in response to immunization. The principal methods are: (1) The determination of the tissues in which the newly formed antibodies are demonstrable before they appear in the blood; (2) the determination of the tissues in which the antigenic substances become fixed; (3) the study of the effects on antibody production of the removal of organs, limited so far almost entirely to splenectomy; (4) the study of the effects of various substances, e. g., arsenical compounds, benzene, etc., of acute anemia, and of the x-ray on antibody fabrication; and (5) the study of the production of antibodies by tissues under cultivation *in vitro*.¹ It is not necessary to say more about the results at this time than that they all point directly to the spleen, the marrow, and the lymphatic tissues as the centers for the manufacture of antibodies. The question arises what influence, if any, on antibody formation is produced by procedures such as the removal of various organs. Through observations of this nature, we possibly may obtain a little better understanding of the very remarkable process of the formation of antibodies.

We have had the opportunity to study the course of specific antibodies educed by the injection of rat blood into dogs from which important organs had been removed by surgical operations. While the material at our disposal was not so large and varied as might be wished, yet the results obtained are not without interest.

It is necessary, in order to determine accurately the effect that certain procedures may have on the production of antibodies, to use reliable standards of comparison. This is particularly true in the case of experiments that might lead to increase or diminution of the total amount of antibodies produced in response to the introduction of fixed quantities of antigen. As the curves described by the increase and

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1. The literature is reviewed by Gay and Rusk, *Tr. Fifteenth Internat. Cong. Hyg. a. Demogr.*, 1912, 2, p. 328.

decrease of newly formed antibodies in the blood serum of different animals seldom run exactly parallel even under the most strictly comparable conditions, isolated measurements, even if made at the time the concentration usually reaches its highest point, do not constitute a safe basis for comparisons from which to draw conclusions. The only safe way is to make frequent determinations so that complete curves can be drawn and compared with the normal standards in each case, namely, the complete course of antibodies in a considerable number of normal animals injected in the same way with the same quantities of antigen. This is the plan we have followed.

From a large series of observations, it has been determined that in adult dogs in ordinary health the injection intravenously of 1 c.c. of a 10 percent suspension of rat blood per kilo of weight is followed by a wave-like production of antibodies that runs a fairly typical and constant course. The particular bodies are the specific opsonin and agglutinin, which run parallel, lysin and precipitin apparently not being produced, except in very small amounts, while no tests have been made for bodies that fix complement. For a day or two after the injection, there sometimes is a fall in the agglutinin and opsonin for rat corpuscles normally present in the serum of the dog. The rise usually begins on the fourth day after the injection, sometimes a day or so later, but very rarely, if ever, earlier. The highest point is reached on the twelfth day as a rule, occasionally a little earlier, hardly ever later. In a few days, a gradual diminution begins, the normal level being reached or closely approached at about the fortieth day after the injection. This general course of the antibodies is illustrated in Table 1. The high point does not seem ever to go beyond a dilution of the serum of 7 to 6144, and very rarely indeed has it been found below a dilution of 1 to 1536.

The measurements are made by finding the highest dilution in which the serum causes undoubted agglutination or opsonification of rat corpuscles in a mixture of 0.6 c.c., containing 0.2 c.c. of a 5 percent suspension of corpuscles, carefully washed, the rest being dog serum and salt solution in the case of the agglutinin tests, and dog serum, salt solution, and a suspension of washed leukocytes in the case of the opsonin tests. The leukocytes are obtained from the pleural exudate of a dog, caused by injecting aleuronat. The mixtures are incubated one hour, and then the results are determined, in the case of the

opsonin tests, by the observation of phagocytosis in properly prepared, stained smears.

In experiments of this kind, special care must be used to exclude dogs with pneumonia (distemper?), because in several instances it has been found that the development of pneumonia in otherwise healthy

TABLE 1

THE EFFECT OF THE REMOVAL OF THE SMALL INTESTINE AND OTHER ORGANS IN DOGS ON THE DEVELOPMENT OF ANTIBODIES FOR RAT CORPUSCLES

Days After Injection of Rat Blood	Control Animal. No Surgical Interference	Removal of Small Intestine 2 Days Before Injection of Rat Blood	Removal of Pancreas and Spleen 2 Days Before Injection of Rat Blood	Removal of Spleen 4 Days After Injection of Rat Blood	Removal of Pancreas 4 Days Before Injection of Rat Blood	Removal of Pancreas 5 Days Before Injection of Rat Blood	Removal of Stomach 7 Days Before Injection of Rat Blood
1	48	48	48	48	96	96	48
2	48	48	48	48	96	96	48
3	48	96	48	48	96	96	48
4	48	96	96	192	192	384	96
5	192	96	96	384	192	384	192
6	768	96	192	768	384	384	192
7	1536	96	384	768	384	384	384
8	1536	96	768	1536	384	384	384
9	1536	192	768	384	384	384	1536
10	3072	384	...	384	Death from intussusception	384	1536
11	3072	768	768	384		384	3072
12	3072	768	768	192		384	3072
13	3072	768	1536	192		384	3072
14	3072	768	768	192		384	1536
15	3072	1536	768	192		384	1536
16	3072	1536		192		384	1536
17	1536	1536				384	768
18	1536	1536				384	768
19	1536	1536				384	768
20	1536	1536				384	768
21	1536	768				384	384
22	1536	768				384	
23	1536	768				384*	
24	1536	768				192	
25	1536	768				96	
26	768	384				96†	
27	768	384					
28	768						
29	768						
30	768						
31	768						
33	768						
36	384						
39	192						

The figures give the highest dilution of the serum causing definite agglutination and opsonification of rat corpuscles.

* Rabies.

† Death.

animals at or about the time of injection of the antigen has inhibited completely or almost completely the formation of antibodies. In this series of experiments, we are confident that pneumonia did not play any part.

The effect of the removal of the stomach, of the pancreas, of the pancreas and the spleen, of the small intestine below the duodenum,

and of other operative procedures on the production of antibodies to rat corpuscles has been studied. In practically all the animals injected soon after the operation, there developed a fairly typical antibody curve, in some cases of rather low range, and in others with some prolongation of the first phase.

Complete removal of the stomach resulted in practically no change in the usual curve after the injection of rat blood.

In one dog from which the pancreas had been removed, death occurred on the thirteenth day, probably on account of an intussusception which had existed for some days. In this animal the amount of antibody produced was much smaller than usual (Table 1). In the case of another dog that was injected with 1 c.c. 10 percent rat blood per kilo on the fifth day after removal of the pancreas, the resulting production of antibody was also comparatively small, but in this case rabies developed and caused death on the twenty-seventh day after the operation (Table 1). It is consequently possible that in this instance the rabic infection may have interfered with the antibodies, altho in experiments on dogs infected with rabies but not subjected to the removal of any organs there seemed to be no diminution in antibody production.

The simultaneous removal of the spleen and pancreas did not reduce the elevation of the curve any more than removal of the spleen alone at about the time of injection of the antigen (Table 1).

Da Costa and Beardsley² found that in diabetic patients the opsonins for streptococci, staphylococci, and tubercle bacilli are reduced very much, as measured by the opsonic index, and Thomas and McPhail³ record that, in pancreatectomized dogs, injection of *Staphylococcus aureus* was not followed by increase in the opsonic index, whereas, in normal dogs, such injection was followed by increase in the index. From these results, which accord well with the diminished resistance of diabetics to infection, the investigators quoted conclude that resistance to infection depends, at least in part, on the activity of the pancreas. As they made their observations in the usual way, that is, with unheated serum, it is possible that the lower index in diabetics and in pancreatectomized dogs results from diminution in the thermolabile opsonic element—complement—rather than from failure of the thermostable element to increase. On this account their results may not warrant the conclusion that in diabetes the power to produce antibodies

2. *Am. Jour. Med. Sc.*, 1908, 136, p. 361.

3. *Proc. Path. Soc., Philadelphia*, 1911, 14, p. 108.

in diminished greatly. Handman⁴ argues that it is the local resistance which is diminished in diabetes, and not the power to form antibodies, but does not produce any experimental evidence in favor of this view. It is unfortunate that, in our experiments, the results of which point to a loss in the power to produce antibodies, we are unable to exclude the possible action of complicating conditions, so that further experiments are required to settle the question definitely.

Removal of the small intestine was made in two dogs. One was injected with rat blood two days later. In both there resulted an average amount of antibody as determined in the usual way; but in the first dog the period of latency was nine days, while in the second it was only four days (Table 1).

Ligation of the mesenteric artery previous to injection of the antigen was followed by a somewhat longer period of latency than usual and a rather small amount of antibody.

When the amount of lymphatic tissue removed in connection with removal of the small intestine or affected by circulatory disturbances of the small intestine, is considered, it hardly seems difficult to understand that the same general effect might follow as seen after removal of the spleen; namely, more or less reduction in the amount of antibody produced. Any cause of the prolongation of the latent period is however not evident.

We have had no opportunity to follow the effects on the antibody curve after removal of parts of the liver in dogs, but in white rats removal of one-half of the liver about twenty-four hours after the introduction of the antigen (sheep blood) was without any demonstrable effect on the amount of lysin produced.

In dogs with Eck's fistula (established by Dr. Miller), the intravenous injection of the usual amount of rat blood was followed by a typical antibody curve. The establishment of the fistula in no way affected the normal antibodies. The observations were all made soon after the fistula was established, and while the animals all appeared to be in good health.

Adrenalectomy in normal dogs, and in dogs at the height of the antibody curve after the injection of rat blood, did not cause any fall in the antibody content of the blood serum, as determined by hourly observations after the operation and until death.

4. Deutsch. Arch. f. klin. Med., 1911, 102, p. 1.

Thyroidectomy immediately after the injection of the antigen, death from tetany occurring on the tenth day, was not followed by any variation in the usual course and amount of antibody production up to that day. This result is in harmony with the results obtained by Fjeldstad⁵ in rabbits, in which thyroidectomy had no influence on the production of agglutinins for typhoid bacilli. Our result is also in harmony with the observation of Launoy and Levy-Bruhl⁶ that in chickens thyroidectomy has no influence on the development and course of spirochetosis gallinarum.

SUMMARY

In the dog, complete removal of the stomach, of the small intestine, or of the thyroid does not interfere with the development of the agglutinin and opsonin for rat corpuscles after intravenous injection of rat blood.

Pancreatectomy, complicated by intussusception and by rabies, resulted in a diminution in the amount of antibodies that accumulated in the blood.

Simultaneous removal of spleen and of pancreas appears to have about the same depressing effect on antibody production in dogs as removal of the spleen only.

Removal of the small intestine and ligation of the mesenteric artery before the injection of rat blood in dogs may be followed by a longer latent period after the injection of antigen than in normal dogs.

Adrenalectomy at the height of the antibody curve in dogs does not change the antibody content of the blood serum.

In rats, removal of about one-half of the liver appears to have no effect on the development of lysin for sheep corpuscles.

The results recorded indicate that the mechanisms for the fabrication of antibodies are quite secure from certain disturbances, and they are in no way contradictory of the current view that these mechanisms are located in the blood-forming organs.

5. *Am. Jour. Physiol.*, 1910, 26, p. 72.

6. *Ann. de l'Inst. Pasteur.*, 1915, 29, p. 213.